REMARKS

Applicants respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 2, 3, 20, 39, 40, 42, 43, 45, 48, and 50 – 52 are cancelled.

Claims 1, 6, 38, and 41 are currently being amended.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1, 4 – 19, 21 – 38, 41, 44, 46, 47, 49, and 53 – 55 are pending in this application.

I. ISSUES

There were three issues raised January 15, 2003 Office Action, all of which are overcome in light of the amendments to the claims and/or the arguments presented herein.

1. Whether a recitation of "a ketone derivative of a saccharide or biosynthetic saccharide precursor" in claims 1, 4-14, 16-18, 38, 41, 44 and 47 encompasses such "a myriad of compounds" that a skilled artisan would not be able to practice the invention across its full scope. More particularly, the issue is whether compounds other than N-levulinoyl mannosamine and N-levulinoyl fucose are enabled.

2. Whether claims 19, 21-27, 29 and 53-55 would have been obvious based on Shih *et al.* (U.S. 5,057,313) taken in view of Leung *et al.* (*Int. J. Cancer* 60:534-538 (1995)) and Qu *et al.* (*Glycobiology* 7:803-809 (1997)).

3. Whether the specification reasonably conveyed to one skilled in the relevant art that the inventors had possession of the invention claimed in claims 8-14, 16-18, 19, 21-27,

29, 44, 46, 47, 49, and 53-55 at the time the application was filed. This rejection relates to the recitation "wherein the reactive ketone group is not introduced by oxidation."

A. Issue 1: recitation of "a ketone derivative of a saccharide or biosynthetic saccharide precursor" allegedly encompassing such "a myriad of compounds" that a skilled artisan would not be able to practice the invention across its full scope.

In their Appeal Brief filed October 15, 2003, Applicants have presented arguments against the examiner's assertions that the phrase "a ketone derivative of a saccharide or biosynthetic saccharide precursor" defines "a myriad of compounds." Thus, those arguments will not be repeated here. Applicants assert, however, that the rejection under 35 U.S.C. § 112, first paragraph of claims 1, 4 – 14, 16 – 18, 38, 41, 44, and 47 enunciated in the January 15, 2003 Office Action has been overcome by the amendments to claims 1, 6, 38 and 41. Reconsideration and withdrawal of the rejection are respectfully requested.

B. Issue 2: Claims 19, 21-27, 29 and 53-55 allegedly obvious based on Shih *et al.* (U.S. 5,057,313) taken in view of Leung *et al.* (*Int. J. Cancer* 60:534-538 (1995)) and Qu *et al.* (*Glycobiology* 7:803-809 (1997)).

Claims 19, 21-27, 29 and 53-55 are rejected under Section 103(a) based on Shih *et al.* U.S. 5,057,313) in view of Leung *et al.*, *Int. J. Cancer*, 60:534-538 (1995) ("Leung I") and Qu *et al.*, *Glycobiology*, 7:803-809 (1997). The examiner urges that Shih *et al.* discloses oxidizing a carbohydrate of an antibody to produce ketones and conjugating drugs and toxins to the oxidized antibody. Shih *et al.* teaches oxidizing a carbohydrate of an antibody to produce ketones and conjugating drugs and toxins to the oxidized antibody. The examiner admits that Shih *et al.* does not teach antibodies with glycosylation sites at the HCN1, HCN5 or Vκ-N site, but alleges that these deficiencies are made up for by the teaching of Leung I and Qu *et al.*

The claims in question recite that "the reactive ketone group is not introduced by oxidation." It is clear that the present application discloses an alternative to introducing reactive groups by oxidizing a sugar. For example, page 2 of the specification discusses Leung *et al.*, *J. Immunol.* 154: 5919 (1995) ("Leung II"), which is exemplary of methods that oxidize a carbohydrate, as follows:

> in order to conjugate at these carbohydrates, the ribose rings must be chemically oxidized to generate reactive aldehyde groups. Aldehyde groups thus formed can be covalently bonded to the amino groups of chelates or drugs through Schiff bases. Since only the C-C bonds with hydroxyl groups attached to each carbon can be periodate-oxidized to form two aldehyde groups, the maximum number of these reactive sites is dictated by the structure and linkages of the oligosaccharide.

The present invention provides glycosylated antibodies that do not require this oxidation, as an alternative to methods like that disclosed in the Leung II and Shih. The present method clearly goes directly from introduction of a ketone derivative onto an antibody to reacting the "resulting antibody" with a ketone reactive group, *i.e.*, the reactive ketone group is introduced as a conjugate to a non-oxidized sugar.

The portion of Shih *et al.* that is cited by the examiner actually is a reference to a published application by McKearn (EP 88,695), which discloses "a method for preparing antibody conjugates which involves oxidizing the carbohydrate portion of the antibody and linking compounds with free amine groups to the resultant carbonyls (aldehyde and/or ketone groups) by Schiff base formation. The harsh oxidation used to open the ring and thereby generate the carbonyl groups, especially where complete oxidation of all carbohydrate residues is desired, and the harsh reducing environment used to stabilize the Schiff base conjugate, both may impair the biological activity of the molecule. By contrast, the antibodies according to the present invention already have a reactive ketone group as a side chain on the carbohydrate used in the glycosylation of the antibody, which is produced by the transfected host cell's biosynthetic machinery. Shih (McKearn) does not disclose a glycosylated antibody or antigen-binding antibody fragment having a reactive ketone group on the glycosylated site that is not introduced by harsh oxidation. In particular, Shih (McKearn) does not disclose such a glycosylated antibody prepared by the method of claim 1.

The examiner urges that "the claims are directed to a product and there is no indication in the specification or the prior art that the structure of the reactive ketone would be different in the oxidized method versus the biosynthetic method." If the ketone used to derivatize the saccharide or saccharide precursor used for glycosylation is not an oxidized sugar, it is clear

that the product is structurally different from the prior art. Furthermore, most oxidized sugars produce aldehydes and not ketones – another clear structural difference from the prior art. Page 3 of the specification explains that the structural profile of hLL2HCN1-carbohydrates reveals that about 2-4 hexose rings in an oligosaccharide chain are available for periodate oxidation, which means that a maximum of 8-16 aldehyde groups on average can be generated from the carbohydrate side chains of each hLL2HCN1 $F(ab')_2$ fragment. With the average size of hLL2HCN5-carbohydrate being 3-4 monosaccharide residues larger than that of HCN1, a higher number of maximum achievable aldehyde groups for hLL2HCN5 is expected. When the oxidizing conditions are mild, only 1.6 and 3 molecules of DTPA can be conjugated to the $F(ab')_2$ of hLL2HCN1 and hLL2HCN5 sites, respectively, due to inefficient oxidation of hexose rings under these conditions. When harsher oxidizing conditions are used to generate more aldehyde groups, the three-dimensional structure of the antibodies is altered and the immunoreactivities of the antibodies may suffer. This would also hold for ketone groups generated by oxidation of glycosylated antibodies. In contrast, the number of glycosylation sites with reactive ketone structures is not limited to those available by oxidation of the oligosaccharide chains. Moreover, the biosynthetic route does not alter the three-dimensional structure of the antibodies. Even if the ketone may not differ in structure, the specification clearly provides a logical basis for why the ***glycosylated antibody*** on which it is contained will be different. Thus, it is reasonable to conclude that the present antibodies are different than those of the prior art.

The addition of Leung I and/or Qu *et al.* to Shih (McKearn) would not have suggested the invention as presently claimed. Leung I discloses a glycosylation site in the Vκ domain and that this site can be used for conjugations. Leung I references other articles which disclose the conjugation technique. Like Shih (McKearn), these entail chemical oxidation of the rings to generate reactive aldehyde groups, which then can be covalently bonded to the amino groups of chelates or drugs through Schiff bases. Since only the C-C bonds with hydroxyl groups attached to each carbon can be periodate-oxidized to form two aldehyde groups, the maximum number of these reactive sites is dictated by the structure and linkages of the oligosaccharide, hence Leung's disclosure that an average of 2 to 6 chelators such as DTPA could be conjugated.

Qu *et al.* teaches the compositions and sequences of CH1-appended carbohydrates from two antibodies, hLL2HCN1 and hLL2HCN5, as determined by fluorophore-assisted carbohydrate electrophoresis (FACE). The structural profile of hLL2HCN1-carbohydrates revealed that about 2-4 hexose rings in an oligosaccharide chain are available for periodate oxidation. Therefore, a maximum of 8-16 aldehyde groups on average can be generated from the carbohydrate side chains of each hLL2HCN1 F(ab')2 fragment. With the average size of hLL2HCN5-carbohydrate being 3-4 monosaccharide residues larger than that of HCN1, a higher number of maximum achievable aldehyde groups for hLL2HCN5 is expected.

Qu *et al.* does not overcome Shih's failure to teach conjugation methods that use introduced reactive ketone groups on the side chains of the glycosylation carbohydrates, as opposed to chemical oxidation of the carbohydrate ring and subsequent covalent bonding of the thus-generated aldehyde groups to the amino groups of chelates or drugs through Schiff bases. Since only the C-C bonds with hydroxyl groups attached to each carbon can be periodate-oxidized to form two aldehyde groups, the maximum number of these reactive sites is dictated by the structure and linkages of the oligosaccharide. As discussed above, chemical oxidation to generate carbonyl groups has significant adverse consequences. When harsh conditions are used to generate the maximum number of such groups, the three-dimensional structure of the antibodies is altered and the immunoreactivities of the antibodies may suffer. And under milder chemical conditions, only 1.6 and 3 molecules of DTPA are conjugated to the F(ab')2 of hLL2HCN1 and hLL2HCN5 sites, respectively, probably due to inefficient oxidation of hexose rings under these conditions.

All of the references cited by the examiner disclose the use of harsh oxidation conditions to convert a glycosylated antibody to a molecule with available carbonyl functions. The antibodies according to the present invention, on the other hand, have a reactive ketone group on a side chain, and are produced by the transfected host cell's biosynthetic machinery. None of the cited references disclose or suggest a glycosylated antibody or antigen-binding antibody fragment having a reactive ketone group on the glycosylated site that is not introduced by oxidation, and more particularly a glycosylated antibody prepared by the method of claim 1. In accordance with the present invention, these antibodies are made

recombinantly by a transfected host cell. The host cell's biosynthetic machinery converts the antibodies so that they have a reactive ketone group. For these reasons, reconsideration and withdrawal of the rejections under Section 103(a) based on Shih *et al.* in view of Leung I and Qu *et al.* are requested.

C. Issue 3: The specification reasonably conveys to one skilled in the relevant art that, at the time the application was filed, the inventors had possession of glycosylated antibodies and antibody fragments having "a reactive ketone group that is not introduced by oxidation," as claimed in claims 8-14, 16-18, 19, 21-27, 29, 44, 46, 47, 49, and 53-55.

In the January 15, 2003 Office Action the examiner raised a new ground of rejection, alleging that the specification does not reasonably convey to one skilled in the relevant art that, at the time the application was filed, the inventors had possession of glycosylated antibodies and antibody fragments having "a reactive ketone group that is not introduced by oxidation." He admits that "while the specification teaches a method that does not require oxidation, the cited work by Leung II is just prior art and background and the specification does not show support for excluding oxidation of the sugar by chemical methods."

It is well established in the case law that an "appellant's specification need not describe the claimed invention *in ipsis verbis* to comply with the written description requirement . . . The test is whether the originally filed specification disclosure reasonably conveys to a person having ordinary skill that applicant had possession of the subject matter later claimed . . . By the very nature of the inquiry under this statutory provision, each case turns on its own specific facts." *Nelson v. Bowler*, 1 USPQ2d 2076, 2078-2079 (Bd. Pat. App. & Int'f (1986). Similarly, "*ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question." *Fujikawa v. Wattanasin,* 93 F.3d 1559, 1570, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996), and "If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." *In re Alton,* 76 F.3d 1168, 1175, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).

The purpose of the written description requirement is to ensure that the applicant has conveyed to those of skill in the art that he or she was in possession of the claimed invention at the time of filing, and the fundamental factual inquiry regarding the adequacy of disclosure is whether an application conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the claimed invention. *See Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). To provide descriptive support, it is not necessary that the application describe the claim limitations exactly. *See e.g. In re Lukach*, 442 F.2d 967, 969 (CCPA 1971) ([T]he invention claimed does not have to be described *in ipsis verbis* in order to satisfy the description requirement of § 112.) Rather, the application need only be sufficiently clear that persons of skill in the art would recognize that the Applicants had possession of the claimed invention. *See In re Wertheim*, 541 F.2d at 263. The description need not be explicit, but may be implicitly or inherently supported in the originally filed disclosure. *Id.* at 1107. Thus, the written description requirement is satisfied when each claim limitation is supported explicitly, implicitly or inherently in the originally filed disclosure. *See* Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶1, "Written Description" Requirement, 66 Fed. Reg. 1099 (2001). A review of whether the specification complies with the written description requirement is conducted from the standpoint of one of skill in the art at the time the application was filed. *See e.g. Wang Labs. V. Toshiba Corp.*, 993 F.2d 858, 865 (Fed. Cir. 1993).

The examiner admits, for the record, that the specification teaches a method that does not require oxidation. He appears to discount his understanding that this is the case, however, because it was gleaned from the background section of the specification, which describes deficiencies with methods such as those disclosed by Leung *et al.* and other documents that use oxidation to introduce reactive groups the cited work by Leung II. As one of skill in this art, the examiner recognized that the present method does not require oxidation, and was developed in order to overcome the deficiencies of prior art methods that used oxidation to introduce reactive groups. A skilled artisan has recognized that appellants were in possession of glycosylated antibodies and antibody fragments that possess "a reactive ketone group that is not introduced by oxidation," and support for this recitation therefore is implicit in appellants' disclosure. Reconsideration and withdrawal of the rejection of claims 8, 14, 16 18, 19, 21 27,

29, 44, 46, 47, 49, and 53 – 55 under the first paragraph of Section 112 for lack of written description are requested.

II. CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By _____
Richard J. Moran
for Stephen B. Maebius
Reg. # 48,735
Attorney for Applicants
Registration No. 35,264

FOLEY & LARDNER LLP
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5143
Telephone: (202) 672-5569
Facsimile: (202) 672-5399